REMARKS

The claims are 1, 4-11 and 47. Claims 12-46 have been cancelled without prejudice or disclaimer. In particular, claims 12-45 were withdrawn from consideration in view of a restriction requirement and are currently the subject matter of a recently filed divisional application. Claims 1, 4-8, 10-11 and 47 have been amended to better define the invention. Entry of this amendment and reconsideration thereof is respectfully requested.

With respect to the amendments, claim 1 has been amended to make clear that the claimed dosage unit is a solid dosage unit having a percent moisture level less than or equal to 8%. Claim 4 has been amended to recite that the moisture level of the solid dosage unit is less than 5%. Support for these changes can be found, for example, at page 7, lines 18-20 of the specification and in original claim 4.

Claim 6 has been amended to include a list of acceptable inhibitors of ester hydrolysis. Support for this change may be found, for example, at page 9, lines 12-14 of the specification. Claim 10 has been amended by deleting the term "suspension" since a suspension is a liquid dosage form. Lastly, claims 6-8, 11 and 47 have been amended so that capitalization of the term "claim" is consistent. None of the changes made herein are new matter.

Claims 6 and 46 stand rejected as allegedly being non-enabling for inhibitors of acid hydrolysis and organic acids as inhibitors of ester hydrolysis, respectively. While not agreeing with the propriety of the Examiner's rejection and solely to expedite prosecution, Applicants have cancelled claim 46 and amended claim 6 to include a list of organic acids. Accordingly, it is respectfully submitted that this rejection is now moot.

Claims 1, 5 and 10-11 stand rejected as allegedly being obvious under 35 U.S.C. §103 over U.S. Patent No. 3,478,070 ("Stein"). Claims 4, 6-9 and 46-47 were rejected as allegedly obvious over Stein in view of Remington, March and Wolfe. Applicants respectfully traverse these rejections, particularly in view of the amendments made herein and the comments set forth below.

Prior to discussing the merits of the rejections, however, Applicants believe it would be helpful to discuss the advantages of the presently claimed invention. The solid dosage unit of 17ß-estradiol-3-acetate of the present invention has been shown to have unexpectedly and significant improved bioavailability over estradiol. See Dr. de Vries Declaration dated November 14, 2003. In addition, the solid dosage unit of the present invention having a low moisture content is particularly stable. Moreover, in a particularly preferred embodiment of this invention, i.e., wherein the solid dosage contains an ester hydrolysis inhibitor, it has been found that the dosage of 17ß-estradiol-3-acetate is particularly stable. It is respectfully submitted that the art of record does not disclose or suggest the presently claimed invention or the advantages associated therein.

Claim 1 has been amended to include the moisture limitation of original dependent claim 4. Accordingly, the Examiner will appreciate that the rejection based solely on Stein is no longer applicable. However, Stein remains the primary reference that the Examiner relies on and therefore it is considered below.

Stein is clearly directed to the process of selectively acylating the 3-hydroxy group of polyhydroxylated steroids. The Examiner relies on the disclosure that d-estradiol-3-acetate, which can be prepared by the disclosed process, may be used in treating menopausal syndrome. The general disclosure that compounds made by the process can be formulated into tablets and capsules is also relied on. It is clear, however, that Stein does not expressly teach the solid dosage form of the present invention.

Moreover, Applicants submit that Stein does not provide the motivation to incorporate 17ß-estradiol-3-acetate in a solid dosage form having a low moisture content. In fact, Stein does not differentiate between solid dosage form and liquid preparation. See col. 6, lines 34-35. In addition, Stein clearly does not suggest that a solid dosage form of 17ß-estradiol-3-acetate would have improved bioavailability compared to a solid dosage form of estradiol.

The disclosures of Remington, March and Wolfe do not remedy the deficiencies of Stein. Remington is directed to granulation processing. There is simply no suggestion of the low moisture level in the solid dosage form of the present invention or the use of an acid as a hydrolysis inhibitor. Wolfe is simply relied on to show the combination of estrogens and progestogens and thus clearly does not overcome the deficiencies of Stein.

The Examiner relies on March for its disclosure that the hydrolysis of esters may be acid catalyzed and that the reaction is reversible. There clearly is no suggestion in March to maintain the water level of the solid dosage form of the present invention at a low level. The Examiner concludes without support that the moisture level of the composition will be optimized because ester is known to be hydrolyzed in the presence of water. However, the Examiner is directed to page 334 first full paragraph of March which states

that "[s]ince OR is a much poorer leaving group than halide or OCOR, water alone does not hydrolyze most esters." It is respectfully submitted that this is contrary to position taken by the Examiner. For the Examiner's supposition to be correct one must assume that a catalyst of ester hydrolysis is also present in the solid dosage form of the present invention. There is simply no suggestion in the cited prior art of that condition.

Moreover, it is respectfully submitted that March does not suggest the inclusion of one of the claim recited acids in the solid dosage form of the present invention. While March does teach in the abstract that adding an acid to the ester of that acid should reduce hydrolysis, March equally teaches that acids may catalyze ester hydrolysis. It is respectfully submitted, that there is no suggestion in March that would have motivated one of ordinary skill in the art to add one of the claim recited acids to a solid dosage form of 17ß-estradiol-3-acetate. Accordingly, it is respectfully submitted that the art of record, whether taken alone or together, does not suggest the presently claimed invention.

Furthermore, even if the Examiner concludes that a prima facie case of obviousness is made out by the cited art, Applicants submit that any such finding is rebutted by the unexpected advantages of the present invention.

First, as discussed in the declaration of Dr. de Vries dated November 14, 2003, there is a significant and unexpected improvement in estradiol bioavailability from 17ß-estradiol-3-acetate tablet compared to estradiol tablet. The Examiner was uncertain if this was a comparison to the closest prior art. Applicants respectfully submit that solid dosage forms of estradiol, which have been known and used, are the closest prior art to the present invention and that clearly the solid dosage form of the present invention has been shown to have an unexpected and significant advantage over that prior art.

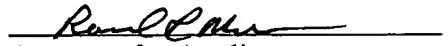
Secondly, with respect to the claims of the present invention that include an

inhibitor of ester hydrolysis, Applicants submit that the evidence of significant and improved stability submitted herewith in a second declaration of Dr. de Vries, also rebutts any prima facie case of obviousness deemed established against those claims. In particular, reference to Dr. de Vries second declaration shows that solid dosage tablets of the present invention containing acetic acid show improved stability over similar tablets that did not contain acetic acid when stored under conditions likely to induce hydrolytic degradation. The improved stability was found both during the manufacture of the tablets and storage. The significant improvement of stability discovered during the manufacture of the solid dosage tablets was particularly unexpected. Accordingly, it is respectfully submitted that the results shown in Dr. de Vries' second declaration clearly support the patentability of at least present claims 6 and 47.

Wherefore, it is respectfully submitted that the art of record, whether taken alone or together, does not disclose or suggest the presently claimed invention. Accordingly, it is respectfully requested that the present amendment be entered, the claims be allowed and the case passed to issue.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,



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